might emerge; but MPTP is a simple molecule consisting of a benzene and a piperidine ring, both of which exist separately in many compounds in plants, animals, and man. For example, some tryptamine metabolites look remarkably close to MPTP. Conceivably, therefore, an environmental source may exist for MPTP or an acquired metabolic defect may produce it or its toxic metabolite in vivo.

The phenomenon of MPTP toxicity has opened up many new testable approaches likely to help us understand parkinsonism and given pharmacologists a superior animal model for searching for better dopaminergic agents and—more important—novel approaches to prevent or slow progression of the disease. Lessons are also apparent for other diseases in which neuronal systems selectively disintegrate.

ADRIAN WILLIAMS

Consultant Neurologist,
Queen Elizabeth Hospital,
Birmingham B15 2TH

1 Davis GC, Williams AC, Markey SP, *et al.* Chronic parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res* 1979;1:249-54.
2 Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983;**219**:970-80.
3 Langston JW, Ballard P. Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): implications for treatment and the pathogenesis of Parkinson's disease. *Can J Neurol Sci* 1984;**11**:160-5.
4 Calne DB, Langston JW. Aetiology of Parkinson's disease. *Lancet* 1983;ii:1457-9.
5 Langston JW, Ballard PA. Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med* 1983;**309**:310.
6 Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc Natl Acad Sci USA* 1983;**80**:4546-50.
7 Langston JW, Forno LS, Rebert CS, Irwin I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res* 1984;**292**:390-4.
8 Heikkila RE, Manzino L, Cabbat FS, Duvoisin RC. Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine by monoamine oxidase inhibitors. *Nature* 1984;**311**:467-9.
8a Markey SP, Johannessen JN, Chiueh CC, Burns RS, Herkenham MA. Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism. *Nature* 1984;**311**:464-7.
9 Lyden A, Bondesson U, Larsson BS, Lindquist NG. Melanin affinity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, an inducer of chronic parkinsonism in humans. *Acta Pharmacol Toxicol (Copenh)* 1983;**534**:29-32.
10 Burns RS, Markey SP, Phillips JM, Chiueh CC. The neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the monkey and man. *Can J Neurol Sci* 1984;**11**:166-8.
11 Bannon MJ, Goedet M, Williams B. The possible relation of glutathione melanin and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (TP) to Parkinson's disease. *Biochem Pharmacol* 1984; **33**:2697-8.
12 Ambani LM, Van Woert MH, Murphy S. Brain peroxidase and catalase in Parkinson's disease. *Arch Neurol* 1975; **32**:114-8.
13 Donaldson J, McGregor D, La Bella F. Manganese neurotoxicity: a model for free radical mediated neurodegeneration. *Can J Physiol Pharmacol* 1982;**60**:1309-405.
14 Heikkila RE, Cohen G. Inhibition of biogenic amine uptake by hydrogen peroxide: a mechanism for toxic effect of 6-hydroxydopamine. *Science* 1971;**172**:1257-8.

Regular Review

Scandinavian model for eliminating measles, mumps, and rubella

ERIK RABO, JOHN TARANGER

Both the individual and society should be protected against measles, mumps, and rubella. Measles is often troublesome for the child and the family, but the main reason for vaccinating against it is the rare but sometimes severe encephalitis. Mumps often causes meningitis and encephalitis and sometimes orchitis and one sided deafness. Rubella is a mild disease but has teratogenic effects.

In a community in which no one has been vaccinated the number of individuals susceptible to a disease increases between outbreaks, and an epidemic starts when enough of them have accumulated. When the epidemic finishes some susceptible people will still remain.

In industrialised countries almost all adults have antibodies against measles, but at the end of an epidemic about one third of children aged under 15 are not immune. In the prevaccination community about a tenth of adults lack antibodies against mumps and about a seventh lack antibodies against rubella. Thus the number of people susceptible to these diseases will be much higher than the number susceptible to measles. For Sweden we have calculated (fig 1) that the number of children and adults without immunity to mumps will never be less than 10 year groups and against rubella 15 year groups—where a year group is the number of people born in one year.

If vaccination manages to reduce the number of susceptible individuals below the minimum number found in the prevaccination community no epidemic will occur and the circulation of the virus may stop. In the short term this is easily accomplished with a one dose programme and a high frequency of vaccination.

In the long term, however, even if one dose vaccination gives lifelong immunity such a programme will build up a susceptible population in older age groups. All individuals will not be vaccinated and all those vaccinated will not become immune. The accumulation of susceptible adults is undesirable—obviously in the case of rubella, since the only

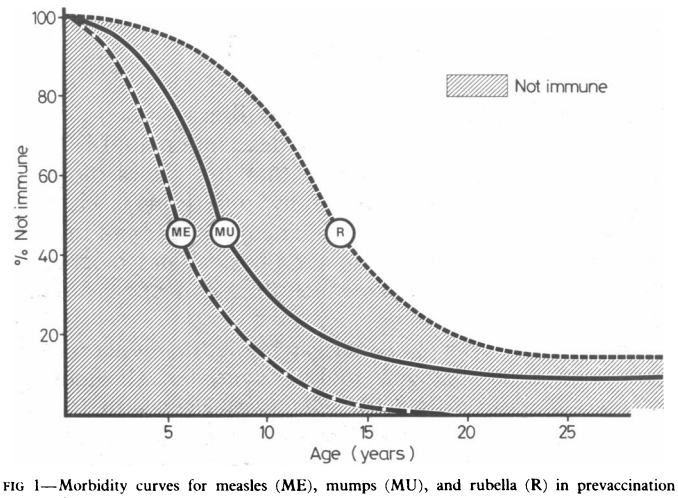

FIG 1—Morbidity curves for measles (ME), mumps (MU), and rubella (R) in prevaccination community.

reason for vaccinating against it is the risk of maternal infection during pregnancy. Mumps is more severe in adults than in children. In Sweden nearly half of all patients with mumps meningoencephalitis treated in hospital and almost all those with orchitis are found among the tenth of adults lacking antibodies.[1] Large numbers of adults with measles have been reported only from isolated communities. During an epidemic in south Greenland almost all of the 4500 inhabitants fell ill. The mortality increased with age, and one in eight over the age of 50 died. Women infected during the first trimester of pregnancy gave birth to children with congenital defects.[2]

Experience with one dose programmes

Planning an effective vaccination programme requires data on the seroconversion rate and the duration of immunity. In principle, yearly, randomised, nationwide serological studies ought to be carried out, but only a few countries are doing this at present—notably Albania[3] and Czechoslovakia.[4] Practically speaking, vaccination against measles, mumps, and rubella will give a seroconversion rate of 90%, though both lower and higher rates have been reported.[5,6] The new stabilised vaccine may give better results.

Maternal antibodies interfere with measles vaccination in children under the age of 1 year. One third of Albanian children vaccinated in 1970 before the age of 1 year lacked detectable antibody titres at the age of 7 years. After revaccination 98% had antibodies against measles.[3] Revaccination has a booster effect when the antibody titres have fallen below a certain level.[4]

In the 1960s immunity after measles vaccination was thought to be life long, but this has not been proved. Krugman has claimed that prospective immunological studies confirm that immunity persists after immunisation as well as after natural infection.[7] The only prospective study with an unvaccinated control group was started by the Medical Research Council in 1964,[8] finding that 16 years after vaccination the incidence of measles was still low.[9] Part of this protection may, however, have been due to their having improved their immunity through contacts with wild measles virus.

Measles was rare in Britain in the 1970s, even in unvaccinated children. This was the result of a policy of vaccination of 1 year old children that began in 1969. Although only half the children have been vaccinated, the incidence of measles is now five times lower than before the start of the programme. The result is that many children have neither had measles nor been vaccinated against it—and so will lack protection as adults.

More reliable information about the duration of the protective effect in a society free from measles is available from Albania, which since 1955 has experienced measles only once—in 1970, when the disease was imported from Yugoslavia by a football team. To avoid a large scale epidemic among those born after 1955, almost half the population —893 000 children under 16—were vaccinated during a campaign lasting three weeks.[3] Ten years later 90% of those vaccinated after the age of 1 year were found still to have antibodies, indicating that immunity from the vaccination was stable. Since 1970 every child in Albania has been vaccinated against measles. Yearly randomised serological studies have shown that about a tenth of those vaccinated lack antibodies—so that even this extremely well run programme will increase the number of susceptible subjects by one tenth of an age class each year.

A similar increase in the number of susceptible young adults has been observed in other vaccinating communities such as the United States, where between 5% and 15% of the college age population is susceptible to measles.[10] This development has led Cherry to warn that "measles and rubella may be time bombs."[11] In Czechoslovakia the morbidity rate of measles in adults was higher in 1981 than before the vaccination started.[12]

Experience with vaccination against mumps is limited but it seems likely to offer the same duration of immunity as that against measles. Since 1968 about half of 1 year olds in the United States have been vaccinated, and this has reduced the incidence of mumps by 90% within eight years. Many children have neither been vaccinated nor had mumps, and the number of susceptible young adults must be presumed to be larger than before vaccination started—a most undesirable development.

Rubella vaccination with available vaccines results in a seroconversion rate of at least 90%. In 10-15% of those vaccinated with the earlier vaccines the titres declined, and some who had low titres from the beginning lost detectable antibodies. After revaccination, however, these individuals showed a typical booster response.[13,14] Studies of clinical efficacy have not indicated diminishing protection over time. Hinman and colleagues state that protection persists for at least 10 years and probably permanently.[13] In a small British study antibodies were still present 16 years after vaccination.[15] The immunity induced by the new vaccine RA 27/3 is better, but long term follow up data are not available.

In 1969 the United States became the first country to introduce mass vaccination of preschool children with the aim of eradicating rubella; the incidence in children under 15 was reduced by more than 80% in 10 years. Accordingly, adults now run a smaller risk of acquiring the disease, and the congenital rubella syndrome has become rare—though between a tenth and a fifth of young American adults still lack antibodies against rubella.[16] One third of all clinical rubella in 1979 occurred in persons aged over 20: men obstetricians have acquired the disease and infected pregnant women.[17] With one dose vaccination of preschool children the number of susceptible adults would increase gradually.

Knox has worked out models to predict the risk of the congenital rubella syndrome with various vaccination programmes. One of these corresponds to the American vaccination programme up to 1979—80% of the 1 year olds vaccinated with a seroconversion rate of 90%.[18] After 10 years of vaccination the risk of congenital rubella syndrome was only one quarter of the initial risk. After 25 years of vaccination, however, the number of susceptible adults will have increased so much that the result will be more congenital rubella syndrome than before the start of the vaccination programme.

Threat to adults

To meet the threats of rubella and measles in adults, the United States has been forced to adopt substantial countermeasures, such as compulsory vaccination of schoolchildren, military personnel, and other groups. Since 1979 great efforts have also been made to vaccinate women of childbearing age against rubella.

Another approach to rubella vaccination—the British

model—is to vaccinate girls just before puberty with the aim of eliminating the congenital rubella syndrome, but not rubella. In Sweden this programme was started in 1975. The effect of vaccination of 12 year old girls has been analysed by Knox (personal communication), who has shown that in spite of great efforts the risk of the congenital rubella syndrome will be reduced by only two thirds by the time the programme reaches a steady state, 20 years after its introduction.

Two dose vaccination programmes

Inevitably, then, one dose vaccination programmes will build up a substantial susceptible population even if every single child is vaccinated. Countermeasures in adults are administratively difficult and expensive. In the United States the overall cost of controlling a measles outbreak in one university was $250 000, and for a rubella outbreak in a hospital $50 000.[19] Furthermore, the compulsory requirements applied in the United States might be unacceptable in Britain[20] and would be politically impossible in Sweden.

These problems may be avoided by vaccinating as many children as possible on two occasions. In 1980 the Swedish Paediatric Association recommended such a programme with a combined measles, mumps, and rubella vaccine.[21] The authorities accepted this programme, and a two dose schedule with vaccination at 18 months and 12 years was implemented in 1982.

The main purpose of the second vaccination is to immunise those who were not vaccinated the first time and those who failed to respond to the first inoculation, but it will also achieve a booster effect in children with low titres. If 90% of the children are vaccinated with 90% efficiency on both occasions, fewer than 5% of the adolescents will lack immunity (fig 2). The total number of susceptibles in the community can never be as large as in the prevaccination community—and the programme will, therefore, prevent accumulation of the number of susceptible individuals necessary to enable epidemics to break out. According to Knox, the two dose programme may be expected practically to eliminate congenital rubella syndrome in 10 years.

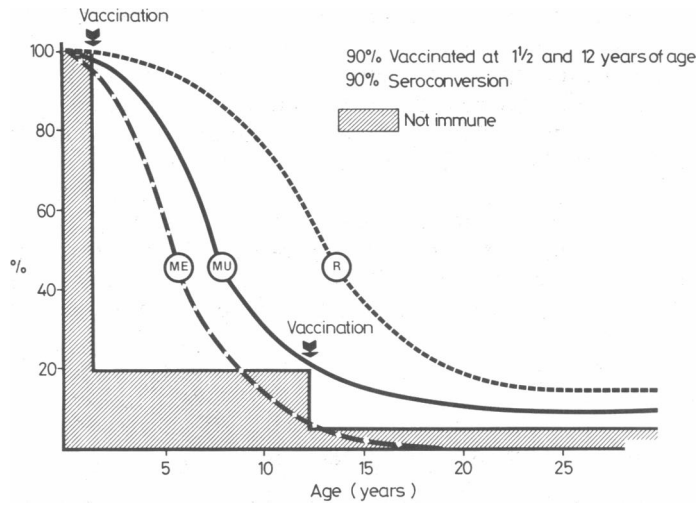

FIG 2—Development of immunity against measles (ME), mumps (MU), and rubella (R) with Swedish two dose vaccination programme. Prevaccination morbidity curves for ME, MU, and R included.

In Sweden the two dose measles, mumps, and rubella programme has been a success from the beginning. The vaccination rate of the first 12 year old age cohort was 88%.[22] Final data are not available on a whole year group of 18 month old children, but preliminary reports indicate a higher vaccination rate than in schoolchildren. Finland and Norway started two dose measles, mumps, and rubella programme soon after Sweden. In Norway the Swedish schedule is applied, while in Finland the second injection is given at the age of 6.

In 1982 in Denmark the health authorities recommended that the Swedish programme should be introduced, but the government has still not agreed to pay for the vaccinations.

ERIK RABO
Paediatrician

JOHN TARANGER
Paediatrician

Paediatric Outpatient Clinic,
Västra Frölunda Hospital,
Gothenburg,

Correspondence to: Dr J Taranger.

1 Bjorvatn B, Skoldenberg B. Parotitmeningit och—orkit i Stockholm—en epidemiologisk bakgrund till vaccinationspolicy. *Lakartidningen* 1978;75:2295-8.
2 Sand Jespersen C, Littauer J, Sagild U. Measles as a cause of fetal defects. *Acta Paediatr Scand* 1977;**66**:367-72.
3 Kakariqi E, Bifska A. Levels of protection against measles years after the introduction of immunization by a very attenuated live measles vaccine. *Bulletin i Universitet te Tiranes* 1980; **11**:63-75.
4 Sejda J. Evaluation of the eight-year period of compulsory measles vaccination in the Czech Socialist Republic (CSSR). *J Hyg Epidemiol Microbiol Immunol* 1979;**23**:273-83.
5 Balfour HH, Amren DP. Rubella, measles and mumps antibodies following vaccination of children. *Am J Dis Child* 1978;**132**:573-7.
6 Brunell PA, Weigle K, Murphy A, Shehab Z, Cobb E. Antibody response following measles-mumps-rubella vaccine under conditions of customary use. *JAMA* 1983;**250**:1409-12.
7 Krugman S. Further-attenuated measles vaccine: characteristics and use. *Rev Infect Dis* 1983;5: 477-81.
8 Miller CL. Measles again. *Br Med J* 1980;**280**:1351.
9 Miller CL. Current impact of measles in the United Kingdom. *Rev Infect Dis* 1983;5:427-32.
10 Amler RW, Kim-Farley RJ, Orenstein WA, Doster SW, Bart KJ. Measles on campus. *J Am Coll Health* 1983;**32**:53-7.
11 Cherry JD. The "new" epidemiology of measles and rubella. *Hosp Prac* 1980;**15**:49-57.
12 Sejda J. Control of measles in Czechoslovakia (CSSR). *Rev Infect Dis* 1983;5:564-7.
13 Hinman AR, Bart KJ, Orenstein WA, Preblud SR. Rational strategy for rubella vaccination. *Lancet* 1983;i:39-41.
14 Böttiger M. Vaccination mot rubella. *Lakartidningen* 1979;**76**:3516-8.
15 O'Shea S, Best J, Banatvala JE, Marchall WC, Dudgeon JA. Persistence of rubella antibody 8-18 years after vaccination. *Br Med J* 1984;**288**:1043.
16 WHO. Rubella surveillance. *WHO Weekly Epidemiological Record* 1984;**59**:49-51.
17 Center for Disease Control. Rubella—United States 1977-1980. *MMWR* 1980;**29**:378-80.
18 Knox EG. Strategy for rubella vaccination. *Int J Epidemiol* 1980;**9**:13-23.
19 Polk BF, White JA, De Girolami PC, Modlin JF. An outbreak of rubella among hospital personnel. *N Engl J Med* 1980;**303**:541-5.
20 Badenoch J. Rubella immunisation: whose baby? *Br Med J* 1984;**288**:564-5.
21 Jonsell R, Broberger O, Brzokoupil K, Noren CE, Rabo E. Vaccination mot mässling, påssjuka och röda hund. *Lakartidningen* 1981;**78**:767-9.
22 Sedvall A, Romanus V, Edman G. Vaccinationsstatus hos svenska skolbarn. *Lakartidningen* 1984;**81**:1633-6.